REMARKS

Claims 1-5 remain pending in the instant application. No amendments have been made. Applicants respond below to the specific rejections set forth in the Office Action mailed November 2, 2004.

Rejection under 35 U.S.C. §101 – Utility

The PTO has maintained the rejection of Claims 1-5 under 35 U.S.C. § 101 as lacking patentable utility for the reasons of record on pages 3 and 4 of the previous Office Action dated May 17, 2004.

Specifically, according to the PTO, Applicants' previous arguments regarding utility were not persuasive. The PTO argues that there is no utility for the claimed antibodies because "their only utility is binding PRO1106 polypeptides, and the PRO1106 polypeptides have no utility." The PTO further asserts that the utility of being a diagnostic target for esophageal tumors is a utility that requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use. The PTO asserts that Example 18 is insufficient because it merely states that the gene encoding PRO1106 polypeptide is "more highly expressed" in one tissue as compared to another. The PTO continues that there is no guidance in the specification as to how high the levels are. Further, the PTO argues that the Declaration of Grimaldi (previously submitted as Exhibit A) does not teach the level of reproducibility or the level of reliability of the results. Surprisingly, the PTO also asserts that "[n]either the specification nor the declarations provide any evidence that indicates what the differences were or whether the results were statistically significant." Also, the PTO argues that Applicants have provided no indication of the nature or number of samples that were used. Therefore, the PTO concludes that the only thing Applicants teach is that the gene was "more highly expressed," and that this does not enable the skilled artisan to differentiate amongst expression levels in order to diagnose any diseases.

The PTO states that "[w]hether or not increased levels of PRO1106 mRNA correlate with increased levels of PRO1106 protein is not an issue," because even if there is a correlation, the antibodies have no utility for the reasons discussed in the preceding paragraph. Thus, according to the PTO, the skilled artisan would still not be able to treat or diagnose any disease.

Applicants respectfully disagree and submit that for the reasons stated below, the nucleic acids encoding the PRO1106 polypeptides, the polypeptides themselves, and the claimed antibodies have a credible, substantial, and specific utility, particularly when the proper utility standard is applied.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility need NOT be proven to an Absolute Certainty – a Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to

> convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> *[I]n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Here, no additional sophisticated testing or further research is required to establish the utility of the claimed antibodies, the PRO1287 polypeptides and the nucleic acids that encode the same in cancer diagnostics. As with *in vitro* testing in the pharmaceutical industry, those of ordinary skill in the art recognize to a reasonably probability that a showing of differential expression of mRNA in cancerous cells compared to normal cells indicates a real world utility in cancer diagnostics for the nucleic acids, their encoded polypeptides and the antibodies to the polypeptides. One of ordinary skill in the art would rely upon the differential expression data in Example 18 as reasonably indicating a real world use for the claimed antibodies. Those of ordinary skill in the art recognize a reasonable

correlation between differential expression in cancerous versus non cancerous cells and utility in distinguishing between those cells.

As in *Cross*, Applicants here do not argue that there is "an invariable exact correlation" between differential expression and diagnostic markers. Instead, Applicants' position detailed below is that the data in Example 18 are reliable and significant, as well as more than sufficient to establish a "significant probability" that the differential expression of the nucleic acids in cancerous versus non cancerous tissue provides diagnostic utility for the same based on "a reasonable correlation therebetween." In order to satisfy the proper utility standard, no further research or testing is required. One of skill in the art more likely than not would recognize utility for the claimed antibodies based upon the differential expression data in Example 18.

Also, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that there is "an invariable exact correlation" between gene expression and protein expression. Instead, Applicants' position detailed below is that a measured differential expression of mRNA in cancer cells establishes a "significant probability" that the encoded polypeptide will also be differentially expressed in the same cancer cells based on "a reasonable correlation therebetween." It is this differential expression of the PRO1106 polypeptide in esophageal tumor cells compared with normal esophageal cells makes the PRO1106 polypeptide useful in the diagnosis of cancer, as it serves as the basis for detecting a difference between the two types of cells.

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not

those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed antibodies to the PRO1106 polypeptides have utility as diagnostic tools for cancer, particularly esophageal cancer. Applicants are not asserting that the claimed antibodies necessarily provide a definitive diagnosis of cancer, but rather that they are useful, alone or in combination with other diagnostic tools to assist in the diagnosis of certain cancers. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1106 polypeptide is more highly expressed in esophageal tumor tissue than in normal esophagus tissue;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, e.g. a decrease, generally leads to a corresponding change in the level of the encoded protein, e.g. a decrease;

3. Given Applicants' evidence that the level of mRNA for the PRO1106 polypeptide is decreased in normal esophagus tissue than in cancerous esophageal tissue, it is likely that the PRO1106 polypeptide is differentially expressed in esophageal tumor, and therefore PRO1106 and antibodies that bind PRO11106 are useful as diagnostic tools to distinguish tumor from normal tissue.

4. The claimed antibodies to PRO1106 polypeptides therefore have utility as diagnostic tools for cancer.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO has challenged the significance and the reliability of the evidence reported in Example 18, and states that these data do not allow a skilled artisan to differentiate amongst expression levels in order to diagnose any disease;

2. The PTO states that whether or not increased levels of PRO1106 mRNA correlate with increased levels of PRO1106 protein is not an issue.

As detailed below, Applicants submit that the PTO has failed to meet its initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). First, the PTO has failed to offer any evidence to support its rejection of the data in Example 18 and the Declaration of Chris Grimaldi in support of these data. Second, Applicants submit that given the well-established correlation between a change in the level of mRNA with a corresponding change in the levels of the encoded protein, the PRO1106 protein is likely differentially expressed in certain tumors. This provides utility for PRO1106 and related proteins and the claimed antibodies as cancer diagnostic tools. Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence to establish that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not statistical or absolute certainty.**

Applicants have established that the Gene Encoding the PRO1106 Polypeptide is Differentially Expressed in Esophageal Cancer compared to Normal Esophagus Tissue

Applicants first address the PTO's argument that the evidence of differential expression of the gene encoding the PRO1106 polypeptide in esophageal tumors is insufficient.

The gene expression data in the specification, Example 18, shows that the mRNA associated with protein PRO1106 was more highly expressed in esophageal tumor tissue than in normal esophagus tissue. Gene expression was analyzed using standard semi-quantitative PCR amplification reactions of cDNA libraries isolated from different human tumor and normal human tissue samples. Identification of the differential expression of the PRO1106 polypeptide-encoding gene in tumor tissue compared to the corresponding normal tissue renders the molecule useful as a diagnostic tool for the determination of the presence or absence of tumor. In support, Applicants previously submitted as Exhibit A, a first Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. This declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue (see Declaration, paragraph 7).

In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Mr. Grimaldi explains that:

> The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. *Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual.* That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. (Paragraph 5) (emphasis added).

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or under-expressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," thus establishing their reliability. He explains that, contrary to the PTO's assertions, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

The PTO argues that Example 18 is insufficient because it does not teach how high the expression level is, what the level of reproducibility or reliability is, whether the results are statistically significant, or the nature or number of samples that were used. The PTO concludes that the disclosure would not enable one of skill in the art to differentiate amongst expression levels to diagnose any disease.

Applicants submit that the declaration of Mr. Grimaldi is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the

experiments at issue. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996).

The PTO has not supplied any reasons or evidence to question the accuracy of the facts upon which Mr. Grimaldi based his opinion. Mr. Grimaldi has personal knowledge of the relevant facts, has based his opinion on those facts, and the PTO has offered no reason or evidence to reject either the underlying facts or his opinion. Therefore, the PTO should accept Mr. Grimaldi's opinion with regard to his statement that "any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue" and that the genes of interest "can be used to differentiate tumor from normal." Together, these statements establish that there is at least a two-fold difference in expression, and that the results are reliable enough that they can be used to distinguish tumor from normal tissue.

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1106 cDNA between esophageal tumor tissue and normal esophagus tissue. Therefore, it follows that expression levels of the PRO1106 gene can be used to distinguish esophageal tumor tissue from its normal tissue counterpart. The PTO has not offered any significant arguments or evidence to the contrary.

As Applicants explain below, it is more likely than not that the PRO1106 polypeptide is also differentially expressed in esophageal tumor tissue, and can therefore be used to distinguish esophageal tumor tissue from normal esophagus tissue. This provides utility for the PRO1106 polypeptides and the antibodies which bind to those polypeptides.

Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

Applicants next turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA for a particular

protein generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1106 polypeptide in esophageal tumor, it is more likely than not that the PRO1106 polypeptide is differentially expressed; and antibodies to proteins differentially expressed in certain tumors have utility as diagnostic tools.

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (previously attached as Exhibit B). As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also previously submitted a copy of the declaration of Paul Polakis, Ph.D. (previously attached as Exhibit C), an expert in the field of cancer biology. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (submitted herewith as Exhibit 1) and (4th ed. 2002) (submitted herewith as Exhibit 2). Figure 9-2 of Exhibit 1 shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Exhibit 1 provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Exhibit 1 at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Exhibit 1 at 453 (emphasis added). Thus, as established in Exhibit 1, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In the 4th Edition of Alberts et al., Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Exhibit 2 at 302 (emphasis added). Similarly, Figure 6-90 on page 364 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Exhibit 2 at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Exhibit 2 at 379 (emphasis added).

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (submitted herewith as Exhibit 3) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Still additional support is found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, submitted herewith as Exhibit 4. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" (see page 4 of Exhibit 4). Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Exhibit 4, page 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." Exhibit 4, page 7.

Further, Meric et al., Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), submitted herewith as Exhibit 5, states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric et al. at 971 (emphasis added).

This statement provides additional support for Applicants' asserted utility. It is true that there is no *necessary* correlation between gene expression and protein expression because there are other mechanisms for regulating gene expression. However, were there no significant correlation between gene expression and protein levels, exploiting differences in gene expression between cancer cells and normal cells would not be a "fundamental principle of molecular therapeutics in cancer." Moreover, as mentioned above, Applicants need not establish a *necessary* connection between gene expression and protein expression. Rather, there need only be a *reasonable* correlation between the evidence offered and the asserted utility such that it is more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true.

Those of skill in the art would not be focusing so much effort on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Taken together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

The fact that the PRO1106 nucleic acids and polypeptides are differentially expressed confers utility upon the claimed antibodies. The Revised Interim Utility Guidelines promulgated by the PTO recognize that proteins which are differentially expressed in cancer have utility. *See* the caveat in Example 12 which state that the utility requirement is satisfied where a protein is expressed in melanoma cells but not in normal skin and antibodies against the protein can be used to diagnose cancer. In addition, while Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO has issued several patents claiming differentially expressed polypeptides and antibodies to the same, or methods employing such antibodies. *See, e.g.,* U.S. Patent No. 6,414,117, U.S. Patent No. 6,124,433, U.S. Patent No. 6,156,500, and U.S. Patent No. 6,562,343 attached hereto as Exhibits 6-9.

As discussed above, Applicants respectfully disagree with the PTO's position that whether or not increased levels of PRO1106 mRNA correlate with increased levels of PRO1106 protein is not an issue. Because it is more likely than not that the PRO1106 protein is also differentially expressed in esophageal tumors, antibodies to the protein can be used as a diagnostic tool for esophageal tumors.

Thus, the PTO's rejection of the second Grimaldi Declaration and Polakis Declaration because they are viewed as insufficient or irrelevant is misplaced. Accordingly, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO1106 mRNA is more highly expressed in esophageal tumor compared to normal esophagus tissue, the PRO1106 polypeptide will have the same expression pattern. This differential expression of PRO1106 and related polypeptides make antibodies to them useful as diagnostic tools.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Antibodies

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed antibodies to PRO1106. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1106 gene and polypeptide in esophageal tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed antibodies.

As discussed above, there are significant data which show that the gene for the PRO1106 polypeptide is more highly expressed in esophageal tumor tissue than in normal esophagus. These data are strong evidence that the PRO1106 gene and polypeptide are associated with esophageal tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1106 gene and polypeptide with a specific disease. The asserted utility as a diagnostic tool for cancer, particularly esophageal tumor, is a specific utility – it is not a general utility that would apply to the broad class of polypeptides.

Conclusion

The PTO has generally asserted the following arguments to support its conclusion that the differential expression of PRO1106 is not sufficient to establish utility for the claimed antibodies: (1) the PTO has challenged the significance and the reliability of the evidence reported in Example 18; and (2) the PTO states that whether or not increased levels of PRO1106 mRNA correlate with increased levels of PRO1106 protein is not an issue. Applicants have addressed each of these arguments in turn.

First, the Applicants provided a first Declaration of Chris Grimaldi stating that the data in Example 18 are real and significant. This declaration also indicates that given the relative difference in expression levels, the disclosed nucleic acids and corresponding polypeptides have utility as cancer diagnostic tools. The PTO has not offered any substantial reason or evidence to question the data in Example 18, or the first Grimaldi Declaration.

Second, Applicants have shown that the second Grimaldi Declaration and Polakis Declaration, the accompanying references, as well as the excerpts and references cited above,

demonstrate that it is well-established in the art that a change in mRNA levels generally correlates to a corresponding change in the encoded protein levels. The PTO has not offered any substantial reason or evidence to question these declarations and supporting references. One of skill in the art will recognize that polypeptides differentially expressed in esophageal tumors and antibodies to those polypeptides have utility as diagnostic tools for esophageal tumors.

Finally, the PTO asserts that there is no asserted specific utility. Applicants have pointed out that the substantial utilities described above are specific to the claimed antibodies because the PRO1106 gene and polypeptide are differentially expressed in esophageal tumors compared to normal esophagus. This is not a general utility that would apply to the broad class of antibodies.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed antibodies as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed antibodies relating to PRO1106 set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112 – Enablement

The Examiner has maintained the rejection of Claims 1-5 under 35 U.S.C. § 112, first paragraph for lack of a specific asserted utility or a well established utility, and therefore, one skilled in the art would not know how to use the claimed invention.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies. Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

Rejection under 35 U.S.C. §102 – Anticipation

The Examiner has maintained the rejection of Claim 1 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,573,095 (the '095 patent). Attached herewith is the Declaration of Audrey Goddard, Paul J. Godowski, J. Christopher Grimaldi, Austin L. Gurney and William I. Wood under 37 C.F.R. §1.131 (referred to hereafter as "the Declaration of Goddard et al."), which establishes that the presently claimed invention antedates the effective date of the '095 patent. The Declaration of Goddard et al. establishes that the presently claimed subject matter was conceived prior to the earliest effective filing date of the '095 patent, April 29, 1998, and diligently reduced to practice on a date after the '095 patent's effective date. Thus, Applicants respectfully submit that the cited reference is not available as prior art, and request that the rejections under 35 USC §102(e) be withdrawn.

As set forth in 37 C.F.R. § 1.131, a patent applicant "may submit an appropriate oath or declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference or activity on which the rejection is based." *See also*, M.P.E.P. § 715. "The affidavit or declaration must state FACTS and produce such documentary evidence and exhibits in support thereof as are available to show conception and completion of the invention in this country ... at least conception being at a date prior to the effective date of the reference." *See* M.P.E.P. § 715.07 (emphasis in original). The showing of facts must be sufficient to show "conception of the invention prior to the effective date of the reference coupled with due diligence from prior to the reference date to a subsequent (actual) reduction to practice." *See id.*

The '095 patent is based upon U.S. Application No. 09/312,283 that was filed on May 14, 1999, which was a continuation-in-part of U.S. Application No.09/188,930, which was filed on November 9, 1998, which application was a continuation-in-part of U.S. Application No. 09/069,726, which was filed on April 29, 1998. Therefore, the earliest possible effective filing date of the '095 patent is April 29, 1998. The '095 patent is cited as a 102(e) reference because it allegedly discloses antibodies to the amino acid sequence of SEQ ID NO:339, which the PTO

argues is 97% identical to the polypeptide of SEQ ID NO:58 from the instant application. However, as set forth below, Applicants were in possession of SEQ ID NO:58 prior to the effective publication date of the '095 patent.

The Declaration and attached Exhibit A demonstrate that the claimed subject matter, particularly a polypeptide having the sequence of SEQ ID NO:58, was conceived by Applicants prior to April 29, 1998. Furthermore, as evidenced by the Declaration and Exhibits B-C, Applicants exhibited diligence in reducing the subject matter of the claims to practice from at least just prior to the '095 patent effective date, by performing various assays to confirm the function of the polypeptide.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §102(e).

Rejection under 35 U.S.C. §103 – Obviousness

The Examiner has maintained the rejection of Claims 2-5 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,573,095 (the '095 patent) in view of U.S. Patent No. 6,480,791 (the '791 patent).

As discussed above, the Declaration of Goddard et al. under 37 C.F.R. § 1.131 submitted herewith establishes that the presently claimed invention antedates the earliest possible effective date of the '095 patent. The declaration and the supporting evidence submitted therewith establish conception of the invention prior to April 29, 1998, and diligent reduction to practice of the invention thereafter. Thus, Applicants respectfully submit that the cited reference is not available as prior art, and the remaining reference, the '791 patent, does not disclose or suggest each and every element of the claims. Therefore, Applicants request that the rejections under 35 USC §103(a) be withdrawn.

Conclusion

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Applicants invite the Examiner to call the undersigned if any issues may be resolved through a telephonic conversation.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 3/30/05

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